

Remarks

**Response to Restriction Requirement and Petition for Reconsideration**

The invention defined by pending claim 27 are specific peptides. The claims which the examiner asserts are drawn to distinct inventions that are "in a materially different form from the immunogenic compositions comprised of the peptides" is clearly in error since the **only** element of pending claim 27 are the peptides themselves. Therefore the invention is not different. The dependent claims do define additional elements- for example, where the peptides are immobilized. However, the search terms must be the same - either the art discloses or makes obvious the same claimed peptides or they do not. Similarly, the peptides of claim 27 must be immunogenic - and therefore must also meet the requirements of the newly added claims that they react with antibodies!

Claims 27-29 have been amended to delete the term "immunogenic composition" and to refer instead to "peptide composition" solely to facilitate rejoinder of the claims.

Reconsideration of the restriction requirement is therefore earnestly solicited. Should the examiner refuse to rejoin and examine the other claims, this request should be treated as a petition and forwarded to the appropriate authority for review. The fee for such a petition may be charged to our deposit order account, noted above.

**Rejections under 35 U.S.C. §102 and/or §103**

Claim 27 was rejected under 35 U.S.C. §102(e) as disclosed by U.S. Patent No. 5,965,353 to Middledorp. Claim 27 was rejected under 35 U.S.C. §102(b) as disclosed by WO 94/06912 to Moddledorp.

Claims 27 and 28 have been amended to more clearly define the peptide as including up to about 40 amino acids, of the portion containing the defined epitopes. Support is found in the application at page 20, lines 26-27, for example. Note that the claimed peptide can be free or bound to a carrier molecule, as described in the application at page 25, line 8.

*U.S. patent No. 5,965,353 to Middledorf; PCT by Middledorf*

The disclosures of the two documents are the same and are therefore discussed as one, although the effective dates as prior art are understood to be different.

Middledorf discloses Epstein Barr virus peptides for use as methods for detecting antibodies to Epstein Barr (not antibodies to human self-antigens which are also cross-reactive with Epstein Barr viral proteins). Sequence ID No. 1 includes more than 120 amino acids, so it is clearly not encompassed by, nor anticipated by, claims 27 and 28 as amended.

Moreover, the patent cannot make obvious the subject matter of claim 27 or 28. There is absolutely no teaching to select for a peptide reactive with autoantibodies, as well as antibody to Epstein Barr virus. The vast majority of antibodies to Epstein Barr virus are reactive with viral proteins only. It took applicants months of careful, selective testing with overlapping octapeptides to define those peptides which elicit an autoimmune response. These cannot be predicted from the general disclosure of Middledorf. In summary, there is no disclosure of the specifically claimed peptides, nor of the properties which are critical to the use of the claimed peptides. Accordingly, one of skill in the art would not be led to select nor to use as claimed, the peptides defined by claims 27 and 28.

**Rejections under 35 U.S.C. §112, first and second paragraph**

Claims 27-29 were rejected under 35 U.S.C. §112, second paragraph, as vague and indefinite. Claims 28 and 29 were also rejected under 35 U.S.C. §112, first paragraph, as non-enabled. These rejections are respectfully traversed.

First, with regard to the scope of the claims, claims 27 and 28 have been amended to clarify that the claims are to EBV-derived peptides of up to 40 amino acids, free or coupled to a carrier molecule. This should obviate the indefiniteness rejection.

With respect to the issue of enablement, the examiner appears to be alleging that there is a requirement that the claimed peptides elicit tolerance to all epitopes. The basis or rationale for this rejection is unclear. There is no legal requirement that a peptide elicit tolerance to all possible epitopes. There is no clinical requirement that a peptide elicit tolerance to all possible epitopes. The only requirement is that the peptides elicit tolerance to one or more epitopes. The examiner has cited no legal or scientific support otherwise.

There is nothing unique with regard to the dosing schedule nor any basis for the examiner concluding that there is. Please identify why there should be a restriction to specific conditions.

Applicants are required to show that the claimed compounds or methods are likely to have the claimed pharmaceutical utility. The data provided in the application and verified by the experiments described in the Declaration under C.F.R. 1.132 by Dr. Harley clearly indicate that the claimed compounds are likely to have an effect on the course of autoimmune diseases.

Autoimmune diseases are associated with the production of antibodies to a variety of epitopes and

the use of these epitopes for desensitization or the use of vaccines absent the epitopes is clearly indicated by the *in vitro* data linking the autoantibodies of autoimmune diseases and the epitopes of the claimed subject matter. The present application clearly establishes the connection between the claimed epitopes and autoimmune diseases. Applicants previously provided a number of references which indicate that the *in vitro* binding data of epitopes involved in autoimmune-type diseases are predictive of *in vivo* use. For example, Nicholson et al. present data that indicate a slightly mutated epitope of the proteolipid protein of myelin acts as an antagonist of the T cell receptor and blocks the binding of the epitope *in vitro* and functions *in vivo* (Nicholson et al., "A T cell receptor antagonist peptide induces T cells that mediate bystander suppression and prevent autoimmune encephalomyelitis induced with multiple myelin antigens" Proc. Natl. Acad. Sci. U S A. 1997 Aug 19;94(17):9279-84). While the *in vivo* mechanisms were not fully elucidated, it was unequivocal that the treatment of the peptide halted the destruction of myelin in mice which is caused by an autoimmune attack on the myelin. Furthermore, Gautam et al. have shown that the herpesvirus *Saimiri* contains small epitopes which when injected into a mouse cause Experimental Autoimmune Encephalomyelitis (EAE) indicating that small epitopes can and do have effects *in vivo*. (Gautam et al., "A viral peptide with limited homology to a self peptide can induce clinical signs of experimental autoimmune encephalomyelitis" J Immunol. 1998 Jul 1;161(1):60-4) Lastly, Vandenbark et al., showed that vaccinations with epitopes related to EAE and Multiple Sclerosis caused protective responses to these diseases *in vivo* (Vandenbark et al., "Effects of vaccination with T cell receptor peptides: epitope switching to a possible disease-

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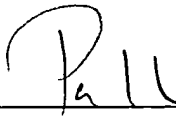
protective determinant of myelin basic protein that is cross-reactive with a TCR BV peptide.”

Immunol Cell Biol. 1998 Feb;76(1):83-90). These publications from 1998 and 1997 support the claims of the present application which claims priority to 1993. There can be little doubt that the methods and compositions of the present claims are fully enabled by the specification.

The Examiner previously indicated that claims drawn to the specific epitopes for induction of tolerance would be allowable. Applicants agreed and added claims 27 and 28 to specifically address this. Why has the examiner now withdrawn this opinion?

Allowance of all claims 27-40, as amended, is earnestly solicited. All claims as pending upon entry of this amendment are attached in an appendix for the convenience of the examiner.

Respectfully submitted,



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Patrea L. Pabst  
Reg. No. 31,284

Date: July 5, 2000  
ARNALL GOLDEN & GREGORY, LLP  
2800 One Atlantic Center  
1201 West Peachtree Street  
Atlanta, GA 30309-3450  
(404) 873-8794  
(404) 873-8795 (fax)

**APPENDIX: Claims as pending upon entry of amendment**

27. (twice amended) [An immunogenic] A peptide composition comprising a peptide molecule selected from the group consisting of PPPGRRP (SEQ ID NO:1), GRGRGRGG (SEQ ID NO:2), RGRGREK (SEQ ID NO:3), GAGAGAGAGAGAGAGAGAGAGA (SEQ ID NO:7), GPQRRGGDNHGRGRGRGRGRGGGRPG (SEQ ID NO:13), GGSGSGPRHRDGVRRPQKRP (SEQ ID NO:14), RPQKRPS (SEQ ID NO:15), QKRPSICIGCKGTHGGTG (SEQ ID NO:16), GTGAGAGARGRGG (SEQ ID NO:17), SGGRGRGG (SEQ ID NO:18), RGGSGGRRGRGR (SEQ ID NO:19), RARGRGRGRGEKRPRS (SEQ ID NO:20), SSSSGSPRRPPPGR (SEQ ID NO:21), RPPPGRRPFFHPVGEADYFEYHQEG (SEQ ID NO:22), PDVPPGAI (SEQ ID NO:23), PGAIEQGPA (SEQ ID NO:24), GPSTGPRG (SEQ ID NO:25), GQGDGGRRK (SEQ ID NO:26), DGGRKKGGWFGKHR (SEQ ID NO:27), GKHRGQGGSN (SEQ ID NO:28), GQGGSNPK (SEQ ID NO:29), NPKFENIA (SEQ ID NO:30), RSHVERTT (SEQ ID NO:31), VFVYGGSKT (SEQ ID NO:32), GSKTSLYNL (SEQ ID NO:33), GMAPGPGP (SEQ ID NO:34), PQGPLRE (SEQ ID NO:35), CNIRVTVC (SEQ ID NO:36), RVTVCSEDDG (SEQ ID NO:37), PPWFPPMVEG (SEQ ID NO:38) and combinations thereof, wherein the peptide comprises up to about forty amino acids and is present either in free form or bound to a carrier molecule.

28. (twice amended) A method comprising administering to a individual a peptide composition comprising a molecule selected from the group consisting of PPPGRRP (SEQ ID NO:1), GRGRGRGG (SEQ ID NO:2), RGRGREK (SEQ ID NO:3), GAGAGAGAGAGAGAGAGAGAGA (SEQ ID NO:7), GPQRRGGDNHGRGRGRGRGRGGGRPG (SEQ ID NO:13), GGSGSGPRHRDGVRRPQKRP (SEQ ID NO:14), RPQKRPS (SEQ ID NO:15), QKRPSICIGCKGTHGGTG (SEQ ID NO:16), GTGAGAGARGRGG (SEQ ID NO:17), SGGRGRGG (SEQ ID NO:18), RGGSGGRRGRGR (SEQ ID NO:19), RARGRGRGRGEKRPRS (SEQ ID NO:20), SSSSGSPRRPPPGR (SEQ ID NO:21), RPPPGRRPFFHPVGEADYFEYHQEG (SEQ ID NO:22), PDVPPGAI (SEQ ID NO:23), PGAIEQGPA (SEQ ID NO:24), GPSTGPRG (SEQ ID NO:25), GQGDGGRRK (SEQ ID NO:26), , GKHRGQGGSN (SEQ ID NO:28), GQGGSNPK (SEQ ID NO:29), NPKFENIA (SEQ ID NO:30), RSHVERTT (SEQ ID NO:31), VFVYGGSKT (SEQ ID NO:32), GSKTSLYNL (SEQ ID NO:33), GMAPGPGP (SEQ ID NO:34), PQGPLRE (SEQ ID NO:35), CNIRVTVC (SEQ ID NO:36), RVTVCSEDDG (SEQ ID NO:37), PPWFPPMVEG (SEQ ID NO:38), and combinations or immunogenic portions thereof, wherein the peptide comprises up to about forty amino acids and is present either in free form or bound to a carrier molecule, and wherein the composition is in a pharmaceutically acceptable carrier for administration of the composition in an amount and mode of administration effective to induce tolerance to EBV-associated immune responses.

29. (amended) The [immunogenic] composition of claim 27 wherein the peptide molecules are in a pharmaceutically acceptable carrier for administration of the composition in an amount and mode of administration effective to induce tolerance to EBV-associated immune responses wherein the composition is in a pharmaceutically acceptable carrier for administration of the composition in an amount and mode of administration effective to induce tolerance to EBV-associated immune responses.

30. The peptide molecules of claim 27 immobilized to a solid support.

31. The peptide molecules of claim 27 labeled with a detectable label.

32. The peptide molecules of claim 30 immobilized to multiwell plates.

33. The peptide molecules of claim 30 immobilized to a gel suitable for affinity chromatography.

34. The peptide molecules of claim 27 bound by autoantibodies in patients characterized by specific disorders.

35. (amended) A method for determining the likelihood that an individual has or will develop an autoimmune disorder comprising screening their antibodies for reactivity with a peptide molecule selected from the group consisting of PPPGRRP (SEQ ID NO:1), GRGRGRGG (SEQ ID NO:2), RGRGREK (SEQ ID NO:3), GAGAGAGAGAGAGAGAGAGAGA (SEQ ID NO:7), GPQRRGGDNHGRGRGRGRGRGGGRPG (SEQ ID NO:13), GGSGSGPRHRDGVRRPQKR (SEQ ID NO:14), RPQKRPS (SEQ ID NO:15), QKRPSICGCKGTHGGTG (SEQ ID NO:16), GTGAGAGARGRG (SEQ ID NO:17), SGGRGRGG (SEQ ID NO:18), RGGSGGRRGRGR (SEQ ID NO:19), RARGRGRGRGEKRPRS (SEQ ID NO:20), SSSSGSPRRPPPGR (SEQ ID NO:21), RPPPGRRPFFHPVGEADYFEYHQEG (SEQ ID NO:22), PDVPPGAI (SEQ ID NO:23), PGAIEQGPA (SEQ ID NO:24), GPSTGPRG (SEQ ID NO:25), GQGDGGRRK (SEQ ID NO:26), DGGRRKKGGWFGKHR (SEQ ID NO:27), GKHRGQGGSN (SEQ ID NO:28), GQGGSNPK (SEQ ID NO:29), NPKFENIA (SEQ ID NO:30), RSHVERTT (SEQ ID NO:31), VFVYGGSKT (SEQ ID NO:32), GSKTSLYNL (SEQ ID NO:33), GMAPGPGP (SEQ ID NO:34), PQGPLRE (SEQ ID NO:35), CNIRVTVC (SEQ ID NO:36), RVTVCSFDDG (SEQ ID NO:37), PPWFPPMVEG (SEQ ID NO:38) and combinations or immunogenic portions thereof, wherein the peptide comprises up to about forty amino acids and is present either in free form or bound to a carrier molecule.

36. The method of claim 35 wherein the peptide molecules are immobilized to a solid support.

37. The method of claim 35 wherein the peptide molecules are labeled with a detectable label.

38. The method of claim 36 wherein the peptide molecules are immobilized to multiwell plates.

39. The method of claim 35 wherein the peptide molecules are immobilized to a gel suitable for affinity chromatography.

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40. The method of claim 35 wherein the peptide molecules are bound by autoantibodies in patients characterized by specific disorders.